

Eigenvalues of neutral networks: interpolating between hypercubes

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Abstract

A neutral network is a subgraph of a Hamming graph, and its principal eigenvalue determines its robustness: the ability of a population evolving on it to withstand errors. Here we consider the most robust small neutral networks: the graphs that interpolate pointwise between hypercube graphs of consecutive dimension (the point, line, line and point in the square, square, square and point in the cube, and so on). We prove that the principal eigenvalue of the adjacency matrix of these graphs is bounded by the logarithm of the number of vertices, and we conjecture an analogous result for Hamming graphs of alphabet size greater than two.

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The eigenvalues of neutral networks—subgraphs of Hamming graphs—is a fascinating subject, yet one which seems to have received little attention from the mathematics community. A recent surge of scientific interest has been motivated by advances in the theory of neutral evolution [1, 2], in which the evolution of a mutating population is captured by spectral properties of its underlying neutral network [3].

A *genome* is the set of all genotypes, or a -ary strings, of length d and alphabet size a . Typically a is small: $a = 2$ (hydrophilic and hydrophobic), $a = 4$ (nucleic acids) or $a = 20$ (amino acids). On the other hand, d can range from 3 (codons) to 10^8 (chromosomes). We represent the genome by a d -dimensional *Hamming graph* $H_{d,a} \equiv (K_a)^d \equiv (K_a \square \dots \square K_a)$, where K_a is the complete graph on a vertices and \square is the Cartesian product [4]. Each of the a^d vertices in the Hamming graph corresponds to a genotype, and two vertices share an edge if the genotypes differ by a single mutation (Hamming distance one). A *neutral network* is the set of genotypes with the same phenotype (observable characteristics); it is just a subgraph of $H_{d,a}$. In this Note we use neutral network and phenotype interchangeably.

Assuming the phenotype has achieved high fitness, adjoining phenotypes will have a relatively negligible growth rate and act as effective absorbing boundaries. Now consider a mutating population on the neutral network. That portion which mutates off of it will be lost, whereas that portion which stays on will survive. The *robustness* r of a neutral network is the long-term probability that a randomly selected individual mutating in a random direction survives. It is the principal eigenvalue λ of the adjacency matrix of the neutral network divided by the number of directions for mutation: $r = \lambda/(d(a-1))$. This Note is about the maximum robustness that a neutral network can have, which for small neutral networks are themselves Hamming graphs and interpolations between them, shown for $a = 2$ in Figure 1. Surprisingly, this ceases to be true for larger neutral networks on longer sequences ($d = 19$ and above),

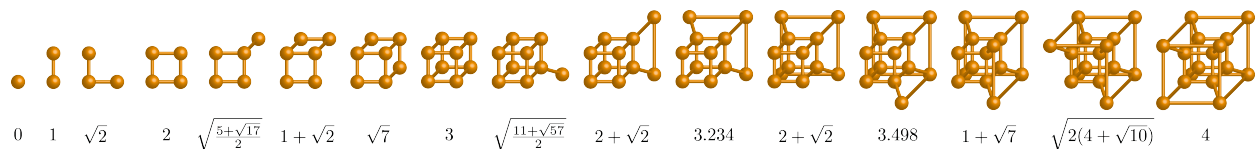


Figure 1: The first 16 “bricklayer’s graphs,” which are the Hamming graphs and the interpolations between them. Below each is the principal eigenvalue of its adjacency matrix.

which we demonstrate by way of counterexamples in the form of star graphs.

This Note is divided into six parts. In the first part, we derive the relation between the robustness r of a neutral network and its principal eigenvalue λ : $r = \lambda/(d(a-1))$. In the second part, we present our main result, $\lambda_n \leq \log_2 n$, where λ_n is the eigenvalue of the n th bricklayer's graph (see Figure 1). We prove it for all values of n apart from $n = 2^d \pm 1$ using a geometric staircase argument. In the third part, we set the stage for the remainder of the proof by constructing polynomials with eigenvalues $\lambda_{2^d \pm 1}$ as roots. In the fourth and fifth parts, we bound the eigenvalues λ_{2^d-1} and λ_{2^d+1} . In the sixth part we conjecture a generalisation of our main result for higher a and conclude with some extensions.

A secondary motivation of this paper is to introduce mathematicians to the connection between neutral networks and spectral graph theory and to encourage them to extend this work.

1. Relation between the robustness and the principal eigenvalue

In this section we derive the relation $r = \lambda/(d(a-1))$, first given in [3]. First, we define the phenotype robustness r as a weighted average over genotype robustness; second, we define it as the extent to which mutation off the neutral network does not deplete the growth due to fitness. Readers who are less interested in the biological motivation may skip this section.

Genotype and phenotype robustness. Consider a neutral network P , and let its adjacency matrix be A . The genotype robustness r_i [1] of a genotype g_i is the probability of a mutation being neutral: the number of neutral edges incident to g_i (i.e. edges which do not lead to a different phenotype) divided by the total number of incident edges $d(a-1)$. The genotype robustness can therefore be written as

$$r_i = \frac{\sum_j A_{ij}}{d(a-1)}. \quad (1)$$

For a neutral network, let $n(t)$ be its population vector at time t , with the i th component $n_i(t)$ corresponding to the population on genotype g_i . The normalized population is distributed according to $n(t)/\sum_i n_i(t)$. Suppose for now that in the limit $t \rightarrow \infty$, the normalized population is distributed according to a unique distribution. Then we define the phenotype robustness r to be the long-time population-weighted average of the genotype robustnesses r_i :

$$r = \frac{\sum_i n_i(\infty) r_i}{\sum_i n_i(\infty)}. \quad (2)$$

It is the fraction of the population flux that is neutral. We will now determine this limit.

Mutational flux and fitness. Mutation induces a population flux across neighbouring genotypes. If the mutation rate per letter is μ , the mutational flux is $1 - (1 - \mu)^{d(a-1)} \approx \mu d(a-1)$ for $\mu d(a-1) \ll 1$. It is the fraction of a population that mutates per generation. Some of this mutational flux will also cross phenotypic boundaries when neighbouring genotypes lie in two different phenotypes. That which does not cross phenotypic boundaries is neutral. The fitness f is the raw reproductive rate of the phenotype. After t generations, the total population of a neutral network will have changed by a factor of f^t , in the absence of mutations.

Mutation matrix. The action of mutation on the population distribution over a single generation can be expressed by the mutation matrix M :

$$M = (1 - \mu d(a-1))I + \mu A. \quad (3)$$

The first term is the probability that no mutation occurs and the second the probability of mutating. Being symmetric, A can be diagonalised by an orthonormal set of eigenvectors x_i :

$$M = (1 - \mu d(a-1)) \sum_i x_i x_i^T + \mu \sum_i x_i v_i x_i^T, \quad (4)$$

where the x_i satisfy the eigenvalue equation $Ax_i = v_i x_i$. The population vector $n(t)$ is obtained by transforming an initial vector n_0 by M^t and multiplying it by f^t :

$$n(t) = f^t M^t n(0) = \sum_i x_i^T n(0) f^t \left(1 - \mu d(a-1) \left(1 - \frac{v_i}{d(a-1)} \right) \right)^t x_i. \quad (5)$$

Let ν_1 be the largest (principal) eigenvalue of A , denoted hereafter λ . Since $|\nu_i| \leq d$, all terms $i > 1$ decay exponentially with respect to the first for $\mu > 0$. In the large time limit the sum is dominated by the first term, whose eigenvalue $\nu_1 \equiv \lambda$ is largest:

$$n_t \approx x_1^\top n(0) f^t \left(1 - \mu d(a-1) \left(1 - \frac{\lambda}{d(a-1)} \right) \right)^t x_1. \quad (6)$$

We now show that defining the robustness as $\lambda/(d(a-1))$ agrees with the definition of phenotype robustness in (2). Indeed, plugging (1) into (2),

$$\begin{aligned} r &= \frac{\sum_{ij} A_{ij} n_i(\infty)}{d(a-1) \sum_i n_i(\infty)} \\ &= \frac{\sum_j \lambda n_j(\infty)}{d(a-1) \sum_i n_i(\infty)} \\ &= \frac{\lambda}{d(a-1)}. \end{aligned}$$

The quantity r therefore measures how well the shape of the neutral network can reduce the rate of deleterious mutation acting on the population as a whole. We see from (6) that at large time t at every generation, a fraction $\mu d(a-1)(1-r)$ of the population mutates off the neutral network, and the growth rate $(1 - \mu d(1-r))f$ is the fitness that can be usefully employed to increase the population and not spent replenishing population lost to deleterious mutations incurred at the boundary. The steady state distribution of the population depends only on the shape of the neutral network and on neither the mutation rate μ nor the fitness f .

2. Neutral networks with large eigenvalues

Bricklayer's graphs. Just how robust a phenotype can be—or how large an eigenvalue a neutral network can have—has remained an open question. For short sequences ($d \leq 4, a = 2$), we found from exhaustive enumeration that the most robust neutral networks are themselves hypercubes or interpolations between them, illustrated in Figure 1. Computational sampling for slightly longer sequences ($5 \leq d \leq 9, a = 2$) agrees with this. We generalize the sequence of graphs and interpolations between them in Figure 1 for $a > 2$ as follows: suppose all vertices $\{q\}$ in $H_{d,a}$ are labelled as integers from 0 to $a^d - 1$, and two vertices share an edge if their base a representations differ in exactly one digit. Then $G_{n,a}$ is the subgraph induced by the vertices $q < n$. We call these graphs $G_{n,a}$ “bricklayer’s graphs” because they form the sequence by which a bricklayer would instinctively fill in the Hamming graph $H_{d,a}$. For the remainder of this Note we set the alphabet size $a = 2$, so we are only concerned with hypercubes and their subgraphs. For simplicity we denote $G_{n,2}$ by G_n . We conjecture an extension of our main result for general a in the Conclusion.

For neutral networks on sequences of short length d , the bricklayer’s graphs G_n are the most robust; they have maximal principal eigenvalues. For longer lengths d , however, a surprise is in store: the G_n are *not* the most robust neutral networks. In particular, we discovered the following counterexamples for $d = 19$ and above. Let S_n be the star graph: a tree with one internal vertex and n leaf vertices. The principal eigenvalue of S_n is readily found to be \sqrt{n} . Now let us compare the eigenvalue of a star of n vertices, S_{n-1} , to the eigenvalue λ_n of G_n . As we prove below, $\lambda_n \leq \log_2 n$. For the bricklayer’s graphs G_n to win, we need $\sqrt{n-1} < \lambda_n$, implying

$$\sqrt{n-1} < \log_2 n.$$

However, this not true for $n \geq 20$. It is an open question as to what shape does maximize the eigenvalue for larger graphs. In the concluding remarks of [5], the authors consider the possibility that Hamming balls (graphs consisting of all points that are most a given distance from a point) are asymptotic maximizers of hypercube subgraphs, but then provide some evidence that they are not.

Our main result. In this Note we prove that the principal eigenvalue λ_n of the bricklayer’s graph G_n satisfies $\lambda_n \leq \log_2 n$. Our general approach is to show by a geometric staircase argument that for $d \geq 3$, a slightly stronger inequality ($\lambda_n < \log_2(n-1)$) holds for most n ; it will then suffice to examine the cases where $n = 2^d \pm 1$, using polynomials that have $\lambda_{2^d \pm 1}$ as roots.

Theorem. For all graphs G_n , we have $\lambda_n \leq \log_2 n$, with equality if and only if n is a power of 2.

Equality is attained in the Theorem if n is a power of 2 since λ_n must lie between the mean and maximum vertex degree [6], and for n a power of 2, all vertices are of degree $\log_2 n$. We wish to show that if n is not a power of 2, there is strict inequality. We make two observations. Observation 1: Since the principal eigenvalue of a proper subgraph of a connected graph is less than the principal eigenvalue of the graph itself, it follows that if $n < m$ then $\lambda_n < \lambda_m$. Observation 2: Since $G_{2n} = G_n \square K_2$, and the spectrum of a Cartesian product of graphs is the sum of their individual spectra [6], it follows that if $\lambda_n < \log_2 n$ then $\lambda_{2n} = \lambda_n + 1 < \log_2 2n$. Using these observations, we claim:

Lemma 2.1. The Theorem is true for all n if for some k ,

$$\lambda_n < \log_2(n-1) \text{ for } 2^k + 2 \leq n \leq 2^{k+1} - 1, \quad (7)$$

and also

$$\lambda_{2^d-1} < \log_2(2^d - 2), \quad d \geq 5, \text{ and} \quad (8)$$

$$\lambda_{2^d+1} < \log_2(2^d + \frac{1}{2}), \quad d \geq 3. \quad (9)$$

Proof. The “staircase” argument is illustrated in Figure 2. We verify numerically that the Theorem is true for $n \leq 16$ and (7) holds for $k = 3$. Now if (7) is true for some k , then by Observation 2,

$$\lambda_{2n} < \log_2(2n-2) \text{ for } 2^k + 2 \leq n \leq 2^{k+1} - 1. \quad (10)$$

By Observation 1 we have the expansion

$$\lambda_{2n-2} < \lambda_{2n-1} < \lambda_{2n} < \log_2(2n-2) < \log_2(2n-1) < \log_2 2n \quad (11)$$

for $2^k + 2 \leq n \leq 2^{k+1} - 1$, so that $\lambda_m < \log_2 m$ for $2^{k+1} + 2 \leq m \leq 2^{k+2} - 2$. Conditions (8) and (9) then ensure that $\lambda_m < \log_2 m$ for $m = 2^{k+1} + 1$ and $m = 2^{k+2} - 1$ as well, proving the Theorem for $2^{k+1} \leq n \leq 2^{k+2}$. Finally, note that (11) together with (8) and (9) imply that (7) holds with k replaced by $k+1$, so we may repeat our induction indefinitely. \square

Therefore, the Theorem reduces to (8) and (9), which we will prove by looking at polynomials that have the eigenvalues of our desired graphs as roots. We will make use of the following standard theorem in linear algebra:

(Cauchy’s Interlacing Theorem [7]). Let A be an $n \times n$ symmetric nonnegative matrix with eigenvalues $a_1 \leq \dots \leq a_n$, and let B be an $m \times m$ principal submatrix of A with eigenvalues $b_1 \leq \dots \leq b_m$. Then for all $j < m+1$, $a_j \leq b_j \leq a_{n-m+j}$.

3. Polynomials with eigenvalues $\lambda_{2^d \pm 1}$ as roots

Let χ_n be the characteristic polynomial of the adjacency matrix of G_n . Enumerating the hypercube spectrum, we find

$$\chi_{2^d}(x) = \prod_{i=0}^d (x - (d - 2i))^{\binom{d}{i}},$$

so we may define the polynomial

$$P_{2^d}(x) = \frac{\chi_{2^d}(x)}{\prod_{i=1}^{d-1} (x - (d - 2i))^{\binom{d}{i}-1}} = \prod_{i=0}^d (x - (d - 2i)). \quad (12)$$

By applying Cauchy’s Interlacing Theorem to the adjacency matrices of $G_{2^{d+1}}$ and G_{2^d} (thus “sandwiching” the spectrum of $\chi_{2^{d+1}}$ by that of χ_{2^d}), we see from the multiplicity of the eigenvalues (of χ_{2^d}) that $\chi_{2^{d+1}}(x)$ has the factor $\prod_{i=1}^{d-1} (x - (d - 2i))^{\binom{d}{i}-1}$. A similar argument shows that $\chi_{2^{d-1}}(x)$ has the same factor. So we may define the polynomials

$$P_{2^d \pm 1}(x) = \frac{\chi_{2^d \pm 1}(x)}{\prod_{i=1}^{d-1} (x - (d - 2i))^{\binom{d}{i}-1}}.$$

Furthermore, we see that χ_{2^d-1} has at most d simple roots, all of which are also roots of the d -degree polynomial P_{2^d-1} .

The reason we use the polynomials P is related to the fact that G_{2^d-1} is a Hamming ball of radius $d-1$ in $H_{d,2}$. We define $B_{d,r}$, the d -dimensional ball of radius r , as the set of points in $H_{d,2}$ that are Hamming distance at most r from the “origin” (the point labelled “0” according to the labelling scheme specified in the first paragraph of section 2). We determine recursive equations that give λ , the principal eigenvalue of $B_{d,r}$. Consider the corresponding eigenvector w , and note that by symmetry the component of w corresponding to a given vertex depends only on the distance of the vertex from the origin. Therefore, let w_k be the value of the component of w corresponding to a vertex of distance k from the origin. By matrix multiplication, we find that

$$\lambda w_0 = d w_1 \quad (13)$$

$$\lambda w_k = k w_{k-1} + (d-k) w_{k+1} \text{ for } 1 \leq k < r \quad (14)$$

$$\lambda w_r = r w_{r-1}. \quad (15)$$

By setting $w_0 = 1$ and following the equations above for each fixed r , we find that the principal eigenvalue of $B_{d,r}$ is a root of the polynomial $p_r(\lambda)$, where $p_0 = \lambda$, $p_1 = \lambda^2 - d$, and

$$p_r = \lambda p_{r-1} - r(d-r+1)p_{r-2} \text{ for } r \geq 2.$$

Applying this to λ_{2^k-1} , we can generate polynomials in λ with coefficients in d (say $f_k(d, \lambda)$) such that when k is substituted for d , the resulting polynomial in λ has λ_{2^k-1} as a root. Then $f_1(d, \lambda) = \lambda$, $f_2(d, \lambda) = \lambda^2 - d$ and, in general,

$$f_k(d, \lambda) = \lambda f_{k-1}(d, \lambda) - (k-1)(d-k+2)f_{k-2}(d, \lambda), \quad (16)$$

and $f_k(k, \lambda)$ has λ_{2^k-1} as a root. In fact, $f_k(k, \lambda)$ has every simple eigenvalue of G_{2^k-1} as a root (by the reasoning of the derivation). Since the degree of $f_k(k, \lambda)$ as a polynomial in λ is d , and we have from above that χ_{2^d-1} has at most d simple roots (all of which are also roots of the d -degree polynomial P_{2^d-1}), it must be the case that

$$P_{2^k-1}(\lambda) = f_k(k, \lambda). \quad (17)$$

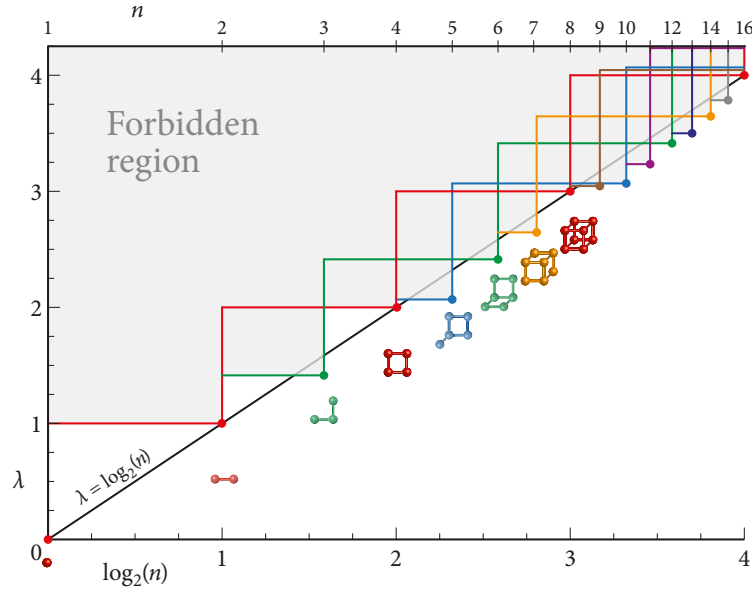


Figure 2: The “staircase” argument for the proof of Lemma 2.1. Because each bricklayer’s graph is a subgraph of its successor, knowing the principal eigenvalue of a bricklayer’s graph immediately places restrictions on higher-dimensional bricklayer’s graphs (as demonstrated by the staircase figures of each color).

4. Bounding λ_{2^d-1}

Rewriting the right side of (8) by applying the Taylor expansion with Lagrange remainder gives

$$\log_2(2^d - 2) = d + \log_2\left(1 - \frac{2}{2^d}\right) > d + \frac{1}{\log 2} \left(-\frac{2}{2^d} - \frac{2^2}{2^{2d-1}}\right).$$

Therefore, for $d \geq 5$,

$$\log_2(2^d - 2) > d - \frac{3}{2} \frac{2}{2^d}. \quad (18)$$

Now we deal with the left side of (8).

Lemma 4.1. $\lambda_{2^d-1} < d - P_{2^d-1}(d)/P'_{2^d-1}(d)$.

Proof. Note that the function $P_{2^d-1}(x)$ is convex on $x \geq \lambda_{2^d-1}$. To see this, let $f(x) = \prod_{i=1}^n (x - r_i)$ be any monic polynomial with all real roots and observe that

$$f''(x) = 2 \sum_{\substack{j_1, j_2=1 \\ j_1 < j_2}}^n \left[\prod_{i=1, i \neq j_1, i \neq j_2}^n (x - r_i) \right],$$

which is always nonnegative if x is at least the largest root of f . Now since the tangent linear approximation of a convex function is an underestimate, we obtain $P_{2^d-1}(d) + P'_{2^d-1}(d) \cdot (\lambda_{2^d-1} - d) < 0$, which implies the lemma. \square

We evaluate the desired values of P_{2^d-1} and its derivative using (17) and the recursive relation in (16).

Lemma 4.2. $P_{2^d-1}(d) = d!$

Proof. Recall the definition of $f_k(d, \lambda)$ from the previous section and the fact that $P_{2^k-1}(\lambda) = f_k(k, \lambda)$. We seek to prove that $f_k(k, k) = k!$, and to do this we will prove a stronger claim that for $i, k \in \mathbb{N}^+$,

$$f_k(i, i) = (i)_k,$$

where $(i)_k = i(i-1)(i-2)\cdots(i-k+1)$ is the Pochhammer symbol. We use induction on k . For $k = 1$ we have $f_1(i, i) = i$ and $f_2(i, i) = i^2 - i = i(i-1)$. Supposing the claim is true for $f_{k-2}(i, i)$ and $f_{k-1}(i, i)$, we find from (16) that

$$\begin{aligned} f_k(i, i) &= i f_{k-1}(i, i) - (k-1)(i-k+2) f_{k-2}(i, i) \\ &= i(i)_{k-1} - (k-1)(i-k+2)(i)_{k-2} \\ &= (i)_k. \end{aligned} \quad \square$$

Lemma 4.3.

$$P'_{2^d-1}(d) = d! \sum_{j=0}^{d-1} \frac{2^j}{j+1}.$$

Proof. With respect to the polynomials $f_k(d, \lambda)$, let $f'_k(d, \lambda)$ denote $\frac{\partial}{\partial \lambda} f_k(d, \lambda)$. Then $P'_{2^k-1}(\lambda) = f'_k(k, \lambda)$, and $f'_1(d, \lambda) = 1$, $f'_2(d, \lambda) = 2\lambda$, and for $k \geq 3$, from (16),

$$f'_k(d, \lambda) = f_{k-1}(d, \lambda) + \lambda f'_{k-1}(d, \lambda) - (k-1)(d-k+2) f'_{k-2}(d, \lambda).$$

We seek to prove that $f'_k(k, k) = k! \sum_{j=0}^{k-1} \frac{2^j}{j+1}$, and to do this we will prove a stronger claim that for integers $k > 0, i \geq 0$,

$$f'_k(k+i, k+i) = k! \sum_{j=0}^{k-1} \binom{k-j+i-1}{i} \frac{2^j}{j+1}.$$

We use induction on k . For the base cases $k = 1$ and $k = 2$ we find that $f'_1(1+i, 1+i) = 1$ and $f'_2(2+i, 2+i) = 2(2+i)$, as desired. Now supposing the claim is true for $f'_{k-2}(k+i, k+i)$ and $f'_{k-1}(k+i, k+i)$, it follows that

$$\begin{aligned}
f'_k(k+i, k+i) &= f_{k-1}(k+i, k+i) + (k+i)f'_{k-1}(k+i, k+i) - (k-1)(i+2)f'_{k-2}(k+i, k+i) \\
&= (k+i)_{k-1} + (k+i)(k-1)! \sum_{j=0}^{k-2} \frac{(k-j+i-1)!}{(i+1)!(k-j-2)!} \frac{2^j}{j+1} - (k-1)! \sum_{j=0}^{k-3} \frac{(k-j+i-1)!}{(i+1)!(k-j-3)!} \frac{2^j}{j+1} \\
&= \frac{(k+i)!}{(i+1)!} + (k-1) \frac{(k+i)!}{(i+1)!} + \sum_{j=0}^{k-2} \left[\frac{(k-1)!}{(k-j-2)!} \frac{(k-j+i)!}{(i+1)!} + j \frac{(k-1)!}{(k-j-2)!} \frac{(k-j+i-1)!}{(i+1)!} \right] \frac{2^j}{j+1} - (k-1)(k-2) \frac{(k+i-1)!}{(i+1)!} - \sum_{j=2}^{k-2} \frac{(k-1)!}{(k-j-2)!} \frac{2^{j-1}}{j} \frac{(k-j+i)!}{(i+1)!} \\
&= \frac{(k+i)!}{(i+1)!} + (k-1) \frac{(k+i)!}{(i+1)!} + (k-1)(k-2) \frac{(k+i-1)!}{(i+1)!} + \sum_{j=2}^{k-2} \left[\frac{(k-1)!}{(k-j-2)!} \frac{2^j}{j+1} + (j-1) \frac{(k-1)!}{(k-j-1)!} \frac{2^{j-1}}{j} \right] \frac{(k-j+i)!}{(i+1)!} \\
&\quad + (k-2)(k-1)! \frac{2^{k-2}}{k-1} - (k-1)(k-2) \frac{(k+i-1)!}{(i+1)!} - \sum_{j=2}^{k-2} \frac{(k-1)!}{(k-j-2)!} \frac{2^{j-1}}{j} \frac{(k-j+i)!}{(i+1)!} \\
&= k \frac{(k+i)!}{(i+1)!} + \sum_{j=2}^{k-2} \left[\frac{(k-1)!}{(k-j-2)!} \left(\frac{2^j}{j+1} - \frac{2^{j-1}}{j} \right) + (j-1) \frac{(k-1)!}{(k-j-1)!} \frac{2^{j-1}}{j} \right] \frac{(k-j+i)!}{(i+1)!} + [2(k-1)(k-1)! - k!] \frac{2^{k-2}}{k-1} \\
&= k \frac{(k+i)!}{(i+1)!} + \sum_{j=2}^{k-2} \frac{k!}{(k-j-1)!} \left(\frac{2^j}{j+1} - \frac{2^{j-1}}{j} \right) \frac{(k-j+i)!}{(i+1)!} + k! \left(\frac{2^{k-1}}{k} - \frac{2^{k-2}}{k-1} \right) \\
&= k! \sum_{j=0}^{k-1} \left[\frac{(k-j+i)!}{(i+1)!(k-j-1)!} \frac{2^j}{j+1} - \frac{(k-j-1)(k-j+i-1)!}{(i+1)!(k-j-1)!} \frac{2^j}{j+1} \right] \\
&= k! \sum_{j=0}^{k-1} \frac{(k-j+i-1)!}{i!(k-j-1)!} \frac{2^j}{j+1}. \quad \square
\end{aligned}$$

Now substituting the results of Lemmas 4.2 and 4.3 into Lemma 4.1,

$$\lambda_{2^d-1} < d - \frac{1}{\sum_{j=0}^{d-1} \frac{2^j}{j+1}}. \quad (19)$$

A simple induction with base cases $1 \leq d \leq 3$ shows that the sum in the denominator of the second term of (19) on the right-hand side can be bounded by

$$\sum_{j=1}^d \frac{2^j}{j} < 3 \frac{2^d}{d}. \quad (20)$$

Therefore,

$$d - \frac{1}{\sum_{j=0}^{d-1} \frac{2^j}{j+1}} < d - \frac{2}{3} \frac{d}{2^d}. \quad (21)$$

Since we may combine the bounds (21) and (18) for $d \geq 5$, we have proved (8).

5. Bounding λ_{2^d+1}

Rewriting the right side of (9) in much the same way as the previous section, we find that for $d \geq 3$,

$$\log_2(2^d + \frac{1}{2}) > d + \frac{1}{2^{2^d}}. \quad (22)$$

As for the left side of (9), we have a computational shortcut:

Lemma 5.1. Let G be a graph, and let e be a bridge of G (i.e., e is an edge such that removing it would increase the number of connected components of G). Let G^* be the graph G with e removed, and G^{**} be the graph G with e and its endpoints removed. Then $\chi_G = \chi_{G^*} - \chi_{G^{**}}$, where χ_G is the characteristic polynomial of the adjacency matrix of G .

Proof. This is an extension of Lemma 1 in [8], which states the result when G is a forest and e is any edge, and is also Theorem 1.3 in [9]. The proof involves expanding the matrix whose determinant is χ_G , using Laplacian expansion and linearity of the determinant. \square

Corollary 5.2. $\chi_{2^{d+1}}(\lambda) = \lambda \chi_{2^d}(\lambda) - \chi_{2^{d-1}}(\lambda)$, and so dividing by $\prod_{i=1}^{d-1} (x - (d - 2i))^{(d-i)-1}$,

$$P_{2^{d+1}}(\lambda) = \lambda P_{2^d}(\lambda) - P_{2^{d-1}}(\lambda).$$

Lemma 5.3. $\lambda_{2^{d+1}} < d - P_{2^{d+1}}(d)/P'_{2^{d+1}}(d)$.

Proof. From the preceding corollary,

$$P''_{2^{d+1}}(x) = 2P'_{2^d}(x) + xP''_{2^d}(x) - P''_{2^{d-1}}(x).$$

We wish to show that this is nonnegative on $x \geq d$. From the argument of the proof of Lemma 4.1, $P'_{2^d}(x) \geq 0$ for $x \geq d$, and from the equation for the second derivative of a polynomial there, $P''_{2^d}(x) > P''_{2^{d-1}}(x)$ for $x \geq d$ since the roots of $P_{2^{d-1}}$ interlace those of P_{2^d} by Cauchy's Interlacing Theorem. So $P_{2^{d+1}}(x)$ is convex on $x \geq d$, and so by linear approximation, $P_{2^{d+1}}(d) + P'_{2^{d+1}}(d) \cdot (\lambda(G_{2^{d+1}}) - d) < 0$, which implies the lemma. \square

Now as in the previous section, we evaluate the desired values of $P_{2^{d+1}}(d)$ and its derivative.

Lemma 5.4. $P_{2^{d+1}}(d) = -d!$.

Proof. Using Corollary 5.2 and Lemma 4.2, $P_{2^{d+1}}(d) = dP_{2^d}(d) - P_{2^{d-1}}(d) = 0 - d!$. \square

Lemma 5.5.

$$P'_{2^{d+1}}(d) = d! \left(d 2^d - \sum_{j=0}^{d-1} \frac{2^j}{j+1} \right).$$

Proof. Differentiating (12) and then plugging in d gives $P'_{2^d}(d) = 2^d d!$. Then using Corollary 5.2 and Lemma 4.3,

$$\begin{aligned} P'_{2^{d+1}}(d) &= P_{2^d}(d) + dP'_{2^d}(d) - P'_{2^{d-1}}(d) \\ &= 0 + d 2^d d! - d! \sum_{j=0}^{d-1} \frac{2^j}{j+1} \\ &= d! \left(d 2^d - \sum_{j=0}^{d-1} \frac{2^j}{j+1} \right). \end{aligned} \quad \square$$

Substituting the results of Lemmas 5.4 and 5.5 into Lemma 5.3,

$$\lambda_{2^{d+1}} < d + \frac{1}{d 2^d - \sum_{j=0}^{d-1} \frac{2^j}{j+1}}. \quad (23)$$

From (20), we obtain that for $d > 1$,

$$d + \frac{1}{d 2^d - \sum_{j=0}^{d-1} \frac{2^j}{j+1}} < d + \frac{1}{(d - \frac{3}{2d})2^d}. \quad (24)$$

Since we may combine the bounds (24) and (22) for $d \geq 5$, we have proved (9).

This concludes the proof of the Theorem.

6. Conclusion

As an additional remark, if we bound $\log_2(2^d - N)$ for general N in the manner of (18), we can deduce an asymptotic result: for any N , there exists D so large that $\lambda_{2^d-1} < \log_2(2^d - N)$ for all $d > D$. Similarly generalizing (22) leads to the result that for any $\epsilon > 0$, there exists D so large that $\lambda_{2^d+1} < \log_2(2^d + \epsilon)$ for all $d > D$.

Throughout most of this paper, we have set $a = 2$. We conjecture an extension of the Theorem for general a :

Conjecture. *For all graphs $G_{n,a}$, we have $\lambda_{n,a} \leq (a - 1) \log_a n$, with equality if and only if n is a power of a .*

There are several interesting and potentially important questions that we have not considered here, which merit further investigation. We prove that the form of the hypercube subgraph with maximal eigenvalue is a bricklayer's graph for small d but the general form of the maximizers is unknown. Indeed it is an open avenue of study to find even non-trivial bounds on the eigenvalue of a hypercube subgraph in terms of its number of vertices. While for small dimension d the bricklayer's graphs are optimal, for $s \geq 20$ and $d \geq s - 1$, Hamming balls of radius 1 are superior. For large s and $d \ll s$, Hamming balls of larger radius may eventually dominate, but this is unproven. How these transitions extend to larger values of alphabet size a is also an open question, though it seems that the critical dimension separating bricklayer's graphs and balls grows with a . We hope that further research by others will shed light on these questions.

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